Beyond "Just Aging": A practical framework for MCI, Biomarkers, and MABs

Nathaniel Chin, MD, Associate Professor of Medicine
Division of Geriatrics, UW School of Medicine and Public Health
Medical Director, Wisconsin Alzheimer's Disease Research Center, Wisconsin Registry for Alzheimer's Prevention (WRAP) Study, & CLARITI Study
Associate Director, UW Geriatric Memory Program

Wisconsin Alzheimer's Disease Research Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Disclosures

- I have received personal fees for consultation and/or advisory board participation from the following pharmaceutical companies: Eisai, Eli Lilly, and NewAmsterdam Pharma
- I am a volunteer board member for the following organizations: Alzheimer's Association and Alzheimer's Foundation of America
- I receive grant funding from the NIH/NIA

Wisconsin Alzheimer's Disease Research Center

Disclosures

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Objectives

- Provide a practical, step-by-step approach to recognizing and evaluating MCI
- Clarify when and how Alzheimer's biomarkers can strengthen diagnostic confidence and translate results into action
- Discuss treatment options, including cognitive and risk-factor interventions, lifestyle interventions (brain health), and monoclonal antibody (MAB) therapies
- Address the value of support, safety planning, and community referrals

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MCI is serious and not normal aging

MCI due to AD is a tipping point stage where smoldering biological changes manifest as symptoms and we can't stop progression

Reality / Hope

MCI is the identify & intervene stage

MCI can be due to non–brain diseases and when reversible causes addressed people can improve

MCI due to AD may be the best stage for MAB intervention to slow progression and modify course

https://tahoequarterly.com/features/walking-a-fine-line

"Getting old is not for the weak"

- Sally is seen in clinic for "memory loss"
- She walks into her living room and can't remember why
- She searches for words during conversations and they come back 5 minutes later
- More distracted than years ago, struggles to multitask, and learning her new iPhone is frustrating
- Symptoms are occasional, not worsening, but bothersome

- Does Sally have MCI?

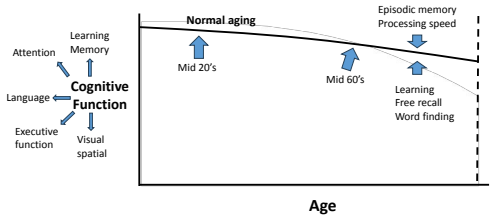
Normal aging vs. MCI

- Cognitive testing is normal
- Normal aging vs. subjective cognitive decline (SCD)
- Evaluate for reversible causes of symptoms and treat

- Do we get a blood biomarker?

- Not yet

Thinking changes in normal aging



Mormino et al. JAD. 2018.

What is normal aging?

- Our brains are best around age 25-30
- We start to notice changes in our thinking around 60-65
- Most common symptoms
  - Forgetfulness of details from prior life events or experiences
  - Slowing of ability to process information
  - More difficulty in learning new information & recalling information without a cue
  - Word finding and difficulty recalling names
- Changes are subtle, occasional, not interfering with daily abilities
- Vocabulary and wisdom tend to increase over time

"There's nothing *mild* in MCI"

- Sally is seen in clinic for "memory loss"
- She forgets details of events from days prior and even complete conversations
- Struggles to find words so often she's now socializing less
- Relies on her GPS for driving, sticky notes are all over her house, and had to attach her house keys to an Apple Airtag
- She doesn't need help with daily activities (medications, finances, cooking) but she's frustrated by her reduced skills
- Symptoms are consistent, persistent and worsening, and family is noticing
- Cognitive testing shows abnormally low scores

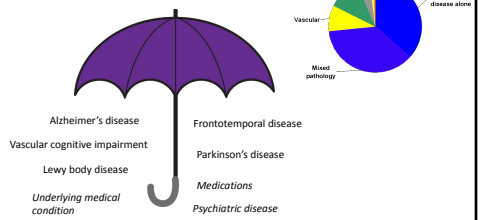
- Why doesn't Sally have dementia?

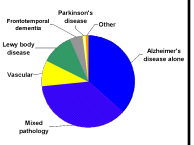
The difference between MCI and dementia is function

Mild Cognitive Impairment	Dementia
Concern regarding change in cognition (mild)	Cognitive loss (mild to severe)
Impairment in 1+ cognitive domains (usually memory)	Impairment in 2+ cognitive domains (usually includes memory)
Preservation of functional independence	*Functionally impaired*
Non-neurodegenerative diseases included	*Primarily neurodegenerative diseases*

Albert MS et al. *Alzheimer's & Dementia* 2011;7:270-279.

Causes of MCI

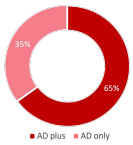




Multi-etiology brain changes are common

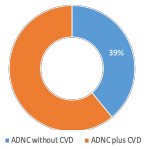
Woodworth et al 2024, Acta Neuropathologica

- 2057 brain donors from NACC
- AD vs AD Plus
  - Plus = LBD and/or TDP43



Frank et al 2022, Neurology

- 2423 brain donors from NACC
- AD vs AD + CVD
  - CVD = moderate to severe



Epidemiology & course of MCI

MCI Prevalence Increases with Age

Age Group	Prevalence
60–64	6.7%
65–69	8.4%
70–74	10.1%
75–79	14.8%
80–84	25.2%

- 5-6% of healthy 70+ year olds will progress to MCI
- 15% of 65+ year olds with MCI progress to dementia over 2 years
- MCI due to AD
  - 8-15% progress to dementia each year
  - Highest risk = amnestic, high amyloid and tau
- 14-38% of MCI converts to unimpaired

Petersen, *Neurology* 2018; 90:1–10.
Petersen, *Continuum* 2016; 22(2):404–418.

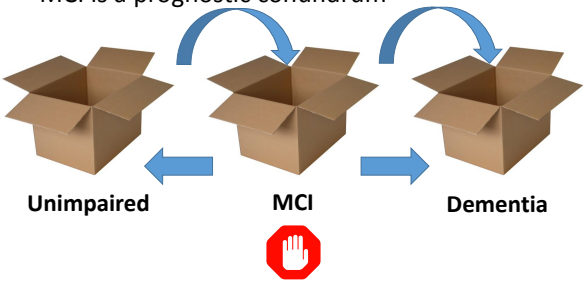
Risk factors for MCI

* Presence of brain disease proteins

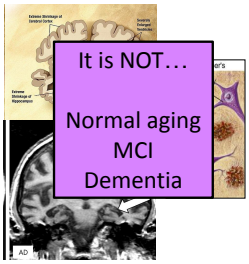
- Age (65+ years old)
- Family history of dementia
- Very low educational attainment
- ApoE-4 allele carrier
- Vascular risk factors (diabetes, hypertension, obesity, dyslipidemia, smoking)
- Cardiovascular disease outcomes (CAD, Afib, CHF, CVD)
- Systemic inflammation and infections
- Mental health conditions (depression, anxiety, apathy)
- Metabolic conditions (thyroid, vitamin B12)
- Sleep conditions

https://my.clevelandclinic.org/health/diseases/17990-mild-cognitive-impairment

MCI is a prognostic conundrum



What is Alzheimer's disease?



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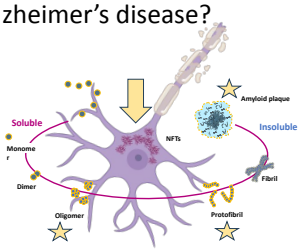
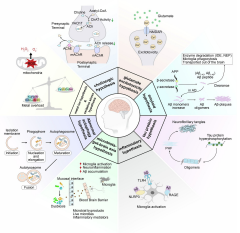


Hampel H, et al. Mol Psychiatry 2021;26(10):5481–5503
d'Errico P, Meyer-Luehmann M. Front Aging Neurosci. 2020;12:265.
Slide courtesy of Eisai Inc.

What are the mechanisms involved in AD?



Zhang et al. *Sig Transduct Target Ther.* 2024.

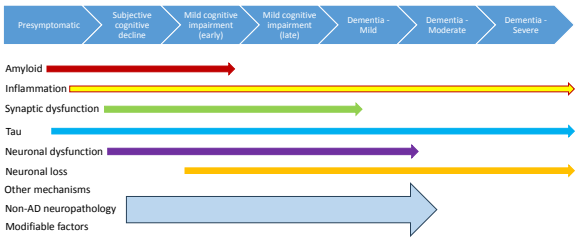
Neuroinflammation
Oxidative stress
Abnormal autophagy
APOE and lipid shuttling
Gut-brain axis

Factors leading to abnormal amyloid build-up

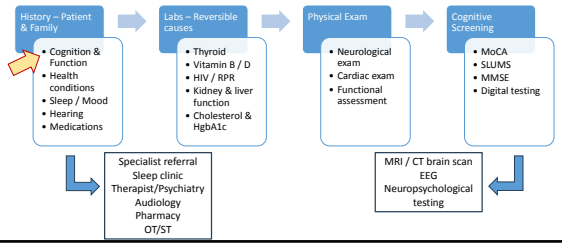
Alzheimer's disease is biology within the brain

- Two hallmark proteins amyloid-β and tau
- Most common cause of progressive cognitive impairment
- Has a prolonged presymptomatic stage ~10-30 years
- Can be identified with PET, CSF, and blood biomarkers
- Co-occurs with other brain diseases

Combining biology with symptoms

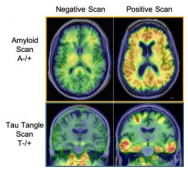


Diagnosing MCI starts with a conversation



What is a biomarker?

Objective measure collected from blood, other body fluids, or tissues that captures normal or abnormal biological processes and conditions



MRI Brain scan from:
Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. Cold Spring Harb Perspect Med. 2012 Apr;2(4):a006213. doi: 10.1101/cshperspect.a006213. PMID: 22474610; PMCID: PMC3312396.

Biomarker Testing Options in ADRD

Imaging
- MRI/CT brain scan
  - Structural & vascular imaging
- PET brain imaging
  - FDG-PET
  - Amyloid
  - Tau
- DAT scan for LBD/PD

Biofluid
- Cerebrospinal fluid
  - Amyloid, ptau and tau
  - Inflammation
  - Markers of neurodegeneration
  - Alpha synuclein for LBD/PD
- Blood
  - Amyloid, ptau, and tau
  - Axonal injury
  - Inflammation

FDA cleared blood biomarkers for AD

Lumipulse G pTau217/B-Amyloid 1-42

- 499 samples from adults with cognitive impairment
- Blood compared to PET scan or CSF test result
- PPV 91.7% with (+) blood test had (+) PET/CSF
- NPV 97.3%
- <20% had indeterminate result

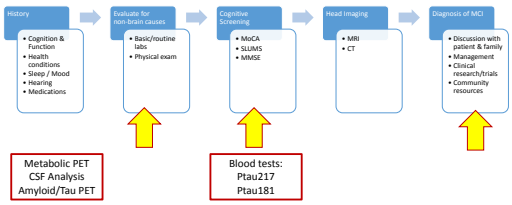
Roche Elecsys pTau181

- 312 participants in non-interventional clinical study
- Participants with cognitive complaint, SCD, or suspected MCI but not official MCI
- 97.9% NPV
- ~46.6% PPV
- For primary care use

https://www.fda.gov/news-events/press-announcements/fda-clears-first-blood-test-used-diagnosing-alzheimers-disease
Wang et al. Alzheimers Dement. 2025.

Roche Product Information

Where do biomarker tests fit?



What is the purpose of the biomarker?

- Support/refute clinical diagnosis
- Monitor disease change
- Determine eligibility for treatment
- Pharmacodynamic/response
- Predict future outcome

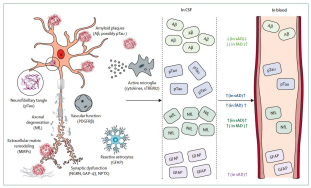
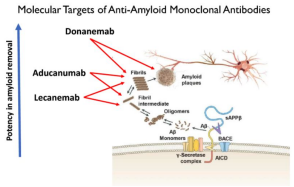


Figure 2: Pathological mechanisms involved in Alzheimer's disease and their associated biofluid-based biomarkers
Alzheimer's disease has a complex pathophysiology. Biofluid-based biomarkers that can be reliably measured in both blood and CSF are Aβ, pTau, NfL, and GFAP. Biomarkers with strong potential in CSF only include cytokines, sTREM2, PSGFBB, MMPs, NGRN, GAP-43, and NPTX. Aβ=amyloid-β. NfL=neurofilament light chain. pTau=phosphorylated tau. GFAP=glial fibrillary acidic protein. MMP=matrix metalloproteinase. sAD=sporadic Alzheimer's disease. EOA=familial Alzheimer's disease.

Teunissen et al. Lancet Neurol. 2022.

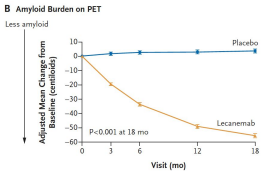
Monoclonal antibody therapy

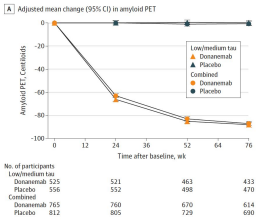


https://www.umc.edu/news/News_Articles/2021/08/How-Monoclonal-antibodies-fight-COVID-19.html

Leisher et al. 2023. CNS Drugs.

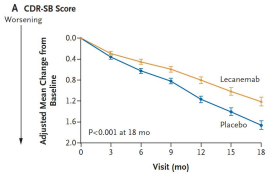
Amyloid targeting therapy effectiveness

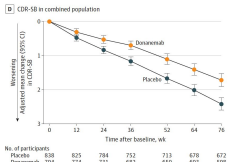




Van Dyck et al. 2023. NEJM.
Leisher et al, 2023; Sims et al, 2023.

Amyloid targeting therapy effectiveness





Van Dyck et al. 2023. NEJM.

Leisher et al, 2023; Sims et al, 2023.

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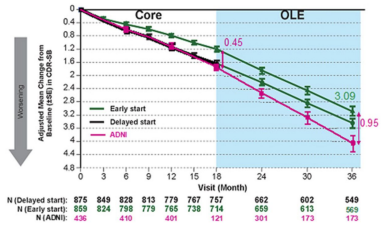
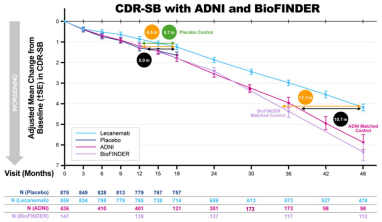


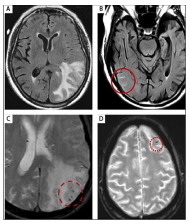
Eisai presentation at AAIC 2025

Amyloid targeting therapy effectiveness



Eisai presentation at AAIC 2025

ARIA is a primary concern and risk



- Imaging finding on MRI brain scan observed in people treated with/not treated with MAB therapy
- ARIA-E: edema in the brain parenchyma or effusions in the sulci
- ARIA-H: hemosiderin deposits representing microhemorrhage in the brain parenchyma or superficial siderosis in the subarachnoid space
- Does not always cause symptoms

ARIA-E = amyloid-related imaging abnormalities due to vasogenic edema, sulcal effusions;
ARIA-H = amyloid-related imaging abnormalities due to microhemorrhages, superficial siderosis.

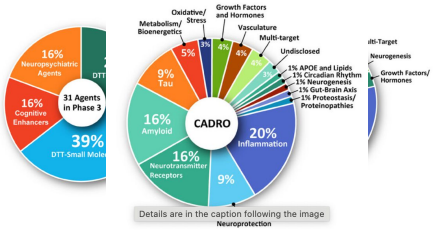
Barakos et al, 2022; Hampel et al, 2023.

ARIA occurs more frequently with treatment

	Donanemab		Lecanemab	
	Most effective dose	Placebo	Most effective dose	Placebo
All ARIA	38.9%	8%	26.6%	9.4%
ARIA-E	26.7%	0.8%	12.6%	1.7%
ARIA-H	30.5%	7.2%	14.0%	7.7%
Death	0.8%	1.6%	0.7%	0.8%

ARIA = amyloid-related imaging abnormalities.
Yadollahikhales et al, 2023; Lilly, 2023.

More than amyloid



Details are in the caption following the image

Cummings et al. Alzheimers Dement. 2025.

Shared decision-making in the clinic

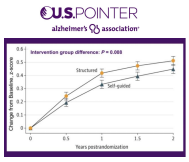
1. Summarizing the evaluation process leading to the diagnosis
2. Communicating with the patient about treatment goals
3. Discussing treatment options, risk/benefits, and the clinician recommendation
4. Reviewing if the patient's decision aligns with stated goals and overall care plan

Shared decision-making requires both clinicians and patients/families talking openly, asking and answering questions, and coming to an understanding related to the decision.

- Alzheimer's Association. Navigating Treatment Options. www.alz.org/alzheimers-dementia/treatments/navigating-treatment-options

Brain health is memory care

- Brain health = optimizing brain abilities = resilience/resistance
- Addressing modifiable causes = medical conditions, medications
- Lifestyle interventions
  - Sleep
  - Daily movement
  - Mental stimulation
  - Avoiding isolation and loneliness
  - Food choices
  - Stress reduction
  - Hearing, vision, teeth



POINTER citation: Baker LD, Espeland MA, Whitmer RA, et al. Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function: The US POINTER Randomized Clinical Trial. JAMA. Published online July 28, 2025. doi:10.1001/jama.2025.12521

Modifiable risk factors for dementia

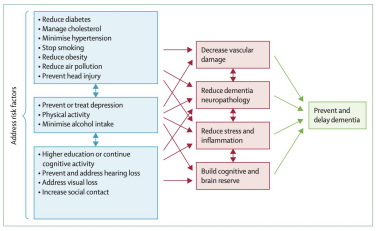


Figure 2: **Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia**

Livingston et al. Lancet. 2024

Follow-up care after a diagnosis of MCI

- Recurrent investigation for additional factors
  - Reversible factors and brain diseases: blood work, brain imaging
- Treatments
  - Brain health, symptomatic medications, novel therapies for AD
- Repeat cognitive testing
- Discussing research opportunities and clinical trials
- Work with OT/ST/PT, counselors
- Legal documents and future life planning

Care management referrals

- Clinical trials
  - Medication-based and lifestyle studies
  - Biomarker studies
- Community organizations
  - Alzheimer's Association
  - AARP (Global Council on Brain Health)
  - Senior centers, in-home service providers
- Aging and Disability Resource Center
  - Dementia Care Specialists
- Specific topic referrals
  - Driving cessation
    - Alzheimer's Association
    - Hartford Foundation
    - State DMV
    - Plan for the road ahead
    - Occupational therapy
  - Cognitive rehab
    - Speech therapy
    - Occupational therapy
  - Incontinence
    - Physical therapy
    - Urology, OB-GYN

Care partners are patients too

- Compared with non-caregiver controls matched by age, gender, race and marital status, caregivers of persons with ADRD experience:
  - 46% more medical visits
  - 71% more prescribed medications
  - Higher diastolic blood pressure
- Care partners experience stress and depression
  - 60% rate stress as high or very high
    - Higher plasma norepinephrine
  - 40% suffer from depression

Haley WE, Levine EG, Brown SL et al. Am J Geriatr Soc. 1987(May); 35(5): 405-411
Shaw et al. J Psychosom Res 2003; 54:293-302
VonKanel et al. Am J of Cardiol 2001(June);87:1405-1408
Grant I; Psychosom Med 1999; 51:420-423

Function is quality of life and safety concerns

- Instrumental ADLs
  - Medication management
    - Overdose, underdose, not taking
  - Financial management
    - Missing payments, overpaying, tax issues, scams
  - Appointments
    - Missing appointments
  - Driving
    - Accidents, violations, getting lost
  - Cooking
    - Burning items, fires
  - Chores
    - Machinery (outside yard work)
- Instrumental ADLs
  - Medication management
    - Supervise, Pharmacy wrapped pillbox
  - Financial management
    - Autopay services, bank assistance, financial POA
  - Appointments
    - Digital calendar, whiteboard
  - Driving
    - OT assessment, restrictions
  - Cooking
    - Closer observation, meal delivery services
  - Chores
    - Hire services

Benefits of an early diagnosis – Patient/Family

- Improves understanding of symptoms, personality & behavioral changes
- May help with acceptance and communication
- Leads to earlier interventions
  - Access to right services and support
  - Referral to community organizations and research
  - Medications
- Facilitates advanced care planning and what is meaningful in life

Dementia Matters explores Alzheimer's disease research and caregiver topics for a general audience

Dementia MATTERS

3 Ways to Listen!

Through your favorite podcast app on your smartphone

Online at adrc.wisc.edu/dementia-matters

On the radio at 102.9 WMUU in Madison, Fridays at 4:00 p.m.

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When Memory Fades: What to Expect at Every Stage, from Early Signs to Full Support for Alzheimer's and Dementia